REMARKS

Status of the Claims

Claims 1, 3-6, 8, and 9-24 are pending. Claim 3 is amended.

Abstract Objection

The Abstract is objected to "because it has not been presented in the proper domestic form." Presumably, this objection is moot in view of the above amendment. Applicants respectfully submit that the Office Action fails to "...point out the defect to the applicant..." as required in M.P.E.P. § 608.01(b). It is not understood from the Office Action what, specifically, is "non-domestic" with respect to the abstract. Nonetheless, the above amendment is believed to place the abstract in better form. Applicants respectfully submit that the Abstract is compliant in that it clearly allows the "United States Patent and Trademark Office and the public generally to determine quickly from a cursory inspection the nature and gist of the technical disclosure." Id.

Accordingly, removal of the objection is respectfully requested.

Issues Under 35 U.S.C. § 112

Claims 1, 3-6, 17, 18, 21, 22, and 24 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement.

This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

As stated in the previous response, this rejection was discussed in detail during the personal interview (21 February 2008). While Applicants respectfully maintain their position regarding the overlap and redundancy in scope, it was agreed that the claims, would be amended to more closely resemble the language of the specification. See, for example, page 3, lines 14-16.

The Office Action appears to base the rejection on the notion "that the terminology '4% or less' encompasses 0% for which there is no support in the specification as originally filed." See page 2 of the Office Action, end of second paragraph. However, the statement "4% or less" does not appear in the claims.

The Office Action further sates that "the specification provides support for... no greater than about 4% by weight of impurities...," but that Applicant does not point out support for the "...terminology now presented in the claims."

Applicants respectfully submit that this assertion is not correct. Present claim 1, for example, incorporates the phrase "at least 95% Amphotericin B and no greater than 5% of impurity products..." Support for this phrase can clearly be found on at least page 3 of the specification. Lines 1-6 indicate that the pharmaceutical composition can comprise substantially pure amphotericin B, wherein "substantially pure" is greater than 90%. 95% clearly falls within this range. There are additionally four examples of "substantially pure" within this range. One of ordinary skill in the art would understand that the impurities percentage of the active ingredient would be affected the amount of substantially pure amphotericin B.

"[T]he 'essential goal' of the description of the invention requirement is to clearly convey the information that an applicant has invented the subject matter which is claimed." In re Barker, 559 F.2d 588, 592 n.4, 194 USPQ 470, 473 n.4 (CCPA 1977). To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.

Of course, with the written description requirement, there is no *in haec verba* requirement, so newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure.

The present Office Action fails to take into account the ranges that one skilled in the art would consider inherently supported by the discussion in the original disclosure, an analysis that is required.

In the past, courts have considered claimed ranges that differ somewhat from the original disclosure. For example, in In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976), the ranges described in the original specification included a range of "25% - 60%" and specific examples of "36%" and "50%." A new claim limitation to "between 35% and 60%" was held to have complied with the description requirement.

Particularly in view of the precedent for allowing ranges such as those claimed, there is nothing in the Office Action that objectively demonstrates why the present claims fail to comply

with the written description as alleged. The burden is on the Examiner to show non-compliance with the written description requirement. See M.P.E.P. § 2163.04, entitled "Burden on the Examiner with Regard to the Written Description Requirement." The Examiner must have a reasonable basis to challenge the adequacy of the written description. No such basis is provided in the Office Action. Additionally, the Examiner must establish a *prima facie* case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed. No such reasons are provided in the instant Office Action.

In the present case, the Office Action even fails to specifically point out the specific claim features that fail to comply. Additionally, Applicants respectfully the inconsistencies in the rejection further indicate an insufficient analysis was completed with respect to what one skilled in the art would consider inherently supported by the discussion in the original disclosure. Claim 3 was decided not to have complied with the written description requirement while claim 8, featuring the same language, was found to have complied.

Accordingly, Applicant's respectfully submit that this rejection should be withdrawn.

Issues Under 35 U.S.C. § 103

Claims 1, 3-6, 8, and 17-24 are rejected under 35 U.S.C. § 103 as allegedly being obvious over Lopez-Berenstein et al. (US '167) in view of US Patent No. 4,902,789 to Michel et al. (US '789), or US Patent No. 4,308,375 to Tang (US '375). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

These references are discussed extensively in the record. As discussed therein, Applicants have pointed out that the Lopez-Berenstein patent fails to even address amphotericin B purity at all in the same terms as the present invention. Lopez-Berenstein is concerned with encapsulation. The Office Action acknowledges that Lopez-Berenstein "...do not disclose purification of amphotericin B." See the Office Action at page 3.

The Office Action attempts to remedy this key deficiency by alleging that one of ordinary skill in the art would be motivated to combine aspects of Lopez-Berenstein with either of the secondary references. More specifically, the Office Action summarily alleges that since purification was well known at the time (as per the Michel et al. or Tang secondary references), one would be motivated to purify the amphotericin B composition of Lopez-Berenstein. The Office Action further states that Applicant's previous arguments "have not been found persuasive because [no] data has been submitted showing the purity of amphotericin achieved by the purification methods achieved by the cited prior art."

Attached is a second Declaration submitted by Dr. Robert Kramer. This Declaration discusses the purification methods of the cited prior art.

With respect to the first secondary reference, Michel et al., the process described therein uses a four-solvent method consisting of methanol, dimethylformamide, methylene chloride and water to solubilize amphotericin B. The Declaration indicates that an analysis of the data provided in the patent document indicates that the process resulted in *improved removal of insoluble content*, an improvement that corresponded with a yield of 97%.

As should be clear by a review of the record, Michel et al., the purity of the resulting amphotericin B (or other antibiotic) product was not directly addressed: the measurement of

"residue on ignition" would not distinguish purity of the amphotericin. Additionally, as described in the attached Declaration, nor would residue on ignition distinguish between amphotericin B and other carbon-based compounds (other polyenes, other antibiotics). Residue on ignition would only provide a measure of the amount of insoluble, inorganic material in the final product.

The Kramer Declaration indicates that in Michel et al., there was no comparison between "residue after ignition" of the starting material and final product after crystallization in Michel's 4-solvent system. Thus, there is no direct evidence that "purification" might have occurred.

As indicated by the Kramer Declaration, the improvement from the process of Michel (as claimed by Michel) is one of more consistent crystallization of product. There was no direct assessment of the composition of organic material or the relative purities of the individual components. Accordingly, Applicants respectfully submit that one of ordinary skill in the art would not view Michel et al. in the manner suggested in the Office Action. Further, there is no indication in the Office Action to suggest otherwise.

Nonetheless, the Declaration provides a demonstration of apparent purity in connection with the Michels et al. process. The Declaration shows an apparent purity of the Michels et al. composition of 91%.[1]

[1] The Examiner's attention is respectfully once again directed to the Declaration of Dr. John Cleary filed May 28, 2008. This Declaration provided examples of the superior and unexpected results of the present invention. In summary, the compositions of the present invention, when compared to prior art preparations, demonstrated an ability to apply a 10-fold higher dose and obtain only about half the renal toxicity. Additionally, the Declaration shows that the mortality rate in infected mice treated with the claimed invention was about half the mortality rate of mice treated with commercial, USP preparations. Additionally, this trend occurs despite the 10-fold greater dose of the composition of the present invention. As indicated in the Declaration, this result is superior and unexpected.

The second "secondary" reference, Tang, is also addressed in the attached Kramer declaration. As stated in the Declaration, Tang describes a method for using ion exchange chromatography to remove gram positive and gram negative bacteria from a methanolic suspension of antibiotics (including, amphotericin B) and bacteria. On the basis of Michel's terminology, the process of Tang is one of decontamination, not purification.

When the reference is considered as a whole, as is required, one of ordinary skill in the art would recognize that the method of Tang would not address separation of amphotericin B from other polyene antibiotics.

As examples, the Examiner's attention is respectfully directed to the following sections of Tang:

> Column 2; lines 14-18: "The resin is found to remove gram negative and gram positive bacteria from the amphotericin. The so-purified amphotericin is then crystallized employing conventional crystallization techniques…"
>
> Column 3; lines 5-12: "After a residence time of 90 seconds the amphotericin rich methanol flowing out of the ion exchange column is found to be substantially free of all gram positive and gram negative bacteria which has been absorbed from the amphotericin by the ion exchange resin. The so-purified amphotericin is then crystallized according to conventional techniques, and filtered, washed and dried."

As stated in the Declaration, it would be clear that in Tang, "purification" only refers to removal of bacteria or their membrane fragments from the methanol suspension. One of ordinary skill in the art would understand that the method of Tang addresses a fundamentally different process than removal of polyenes and other soluble compounds that are present as impurities from amphotericin B.

Thus, the assertion in the Office Action that the present invention would be obvious based on purification as disclosed in Tang has no merit.

In summary, amphotericin B, other polyenes and, in fact, any other compound soluble in methanol are not separated by the ion exchange process disclosed by Tang. Tang, as well as the Office Action, gives no technical reason to the contrary. Thus, Applicants respectfully submit that there is no basis in the prior art references that the claimed compositions would be obvious, particularly since it is clear that the "purification" methods relied on are not appropriate to arrive at the instant claims.

The Kramer Declaration provides evidence that the purification process used therein would not result in a product having the claimed purity levels. One reason, of course, is that the ion exchange process will not work to obtain the claimed purity levels. There is no objective, reasoned statement in the Office Action to suggest otherwise.

Thus, the Office Action fails to present a *prima facie* case of obviousness because there is no established relationship between the cited prior art and claimed invention.

Secondary Considerations

In addition to the lack of a *prima facie* case of evidence, there is additional secondary evidence to be considered by the USPTO. "Secondary evidence" must be evaluated by the USPTO when considering a case of obviousness. Secondary evidence can include evidence of long-felt but unsolved needs, failure of others, and unexpected results. The evidence may be included in the specification as filed, or be provided in a timely manner at some other point during the prosecution.

The superior and unexpected results of the present invention are discussed herein, and throughout the prosecution of this application. Additionally, it should be clear that the present invention helps solve a long-felt need.

As stated in the Specification, traditional amphotericin B induces serious adverse reactions. See the Specification at page 1.

> Amphotericin B is used primarily an intravenous agent in the treatment of severe fungal infections.
>
> However, its usefulness is compromised by a high incidence of adverse effects [flu-like symptoms (fever, chills, myalgias), capillary leak syndrome (hypotension, decreased organ perfusion), pulmonary congestion, changes in mental status (lethargy, confusion, agitation), renal dysfunction with secondary hypokalemia, hypomagnesemia and anemia, and liver dysfunction]. These adverse reactions are observed in up to seventy percent of treated patients. The mechanisms responsible for these reactions are, to date, not entirely known.

Yet, today (and for the past 40 years) amphotericin B remains the best or only alternative for critically ill patients.

Excerpts from the Amphotericin B the boxed warning include the following:

> **CONTRAINDICATIONS**
>
> This product is contraindicated in those patients who have shown hypersensitivity to amphotericin B or any other component in the formulation unless, in the opinion of the physician, the condition requiring treatment is life-threatening and amenable only to amphotericin B therapy.
>
> **WARNINGS**
>
> Amphotericin B is frequently the only effective treatment available for potentially life-threatening fungal disease. In each case, its possible life-saving benefit must be balanced against its untoward and dangerous side effects.

PRECAUTIONS

Amphotericin B should be administered intravenously under close clinical observation by medically trained personnel. It should be reserved for treatment of patients with progressive, potentially life-threatening fungal infections due to susceptible organisms (see INDICATIONS AND USAGE).

Acute reactions including fever, shaking chills, hypotension, anorexia, nausea, vomiting, headache, and tachypnea are common 1 to 3 hours after starting an intravenous infusion. These reactions are usually more severe with the first few doses of amphotericin B and usually diminish with subsequent doses.

Rapid intravenous infusion has been associated with hypotension, hypokalemia, arrhythmias, and shock and should, therefore, be avoided (see DOSAGE AND ADMINISTRATION).

Amphotericin B should be used with care in patients with reduced renal function; frequent monitoring of renal function is recommended (see PRECAUTIONS, Laboratory Tests and ADVERSE REACTIONS). In some patients hydration and sodium repletion prior to amphotericin B administration may reduce the risk of developing nephrotoxicity. Supplemental alkali medication may decrease renal tubular acidosis complications.

Since acute pulmonary reactions have been reported in patients given amphotericin B during or shortly after leukocyte transfusions, it is advisable to temporally separate these infusions as far as possible and to monitor pulmonary function (see PRECAUTIONS, Drug Interactions).

Leukoencephalopathy has been reported following use of amphotericin B. Literature reports have suggested that total body irradiation may be a predisposition.

Whenever medication is interrupted for a period longer than seven days, therapy should be resumed by starting with the lowest dosage level, e.g., 0.25 mg/kg of body weight, and increased gradually as outlined under DOSAGE AND ADMINISTRATION.

Amphotericin B is used to treat a variety of life threatening infections despite very serious and dangerous side effects. By discovering the source of the side effects, the present inventors have met a long-felt need in allowing a safer product.

This was previously not known, and is surprising when compared to the many prior attempts to formulate a safer amphotericin B product. The encapsulation techniques discussed in the record represent the failure of others to formulate a safer amphotericin product.

As stated in the Declaration of Dr. John D. Cleary (filed May 28, 2008), the preset invention, when compared to commercial, USP preparations, demonstrated an ability to apply a 10-fold higher dose and obtain only about half the renal toxicity. The Declaration further showed that the mortality rate in infected mice treated with the claimed invention was about half the mortality rate of mice treated with commercial, USP preparations. This rate occurred despite the 10-fold grater dose of the composition of the present invention. Not only does this result reinforce the long-felt need aspects of a safer treatment, but in addition shows the unexpected and superior results of the present invention.

Additionally, there is another long-felt need addressed by the present invention. The cost to the patient of amphotericin B is extremely expensive. See paragraph 11 of Dr. Cleary's Declaration:

> The cost of AmB-induced events was $29,823 per case. The use of lipid-based formulations of AmB, secondary to their lower risk for nephrotoxicity, is replacing conventional AmB therapy for treatment of systemic fungal infection except in many HIV-infected and pediatric patients. Yet, the cost of comparable therapy is considerably greater for the lipid formulation; daily cost for AmB averages $25, whereas that for lipid-formulated AmB ranges between $450 and $1850. Assuming a 14-day course of therapy, a patient will pay an average of $7000 more for a lipid-based, albeit safer, AmB product. Thus, the present invention can provide a significant improvement over what is currently available. Given the superior and unexpected improvements of the present invention over previous attempts to make AmB treatment safer, the present invention can potentially increase the number of treatment candidates, and allow for increased dosages with reduced side effects.

Applicant's respectfully submit that after considering the secondary evidence, the outstanding rejection should be withdrawn.

Summary of Declaration Evidence

As stated above, this attached Declaration is the second one filed by Dr. Kramer in connection with the instant application. Applicants have submitted three Declarations at separate points in the prosecution , each to address specific questions raised by the Examiner.

The first Declaration was in response to the Office Action mailed April 23, 2007. That Office Action, like the present one, raised the issue of the Michel et al. and Tang patents providing "purification" motivation. The Kramer Declaration was filed in response to the statement in the Office Action that "applicant has not provided any evidence in verified form showing that the references' [Michel et al., US '789 and Tang '375] purification process would not result in a product having the claimed purity levels." The first Declaration reinforces what is clear from the record: the "purification" descriptions relied upon in the Office Action could not confirm the presence of, or lack of, the harmful polyene/endotoxin contaminants addressed by the present invention.[2] The first Kramer Declaration (as well as the present one) provides

[2] Applicants respectfully maintain that requiring such evidence improperly shifts the burden of persuasion to the Applicants. Until the requirements for establishing a *prima facie* case of obviousness are met, there is no duty or need for the Applicants to present further evidence. There has been no objective evidence presented to rebut Applicants arguments (which include Declaration evidence) that one of ordinary skill in the art would not look to the cited references in the manner submitted in the Office Action. The response filed with this Declaration included a discussion of relevant case law demonstrating where the Federal Circuit and Board of Appeals have made decisions that would favor the Applicants in similar situations.

evidence that the purification process of the cited prior art would not result in a product having the claimed purity levels.

The second Declaration (submitted by Dr. John Cleary) was filed with the response to the Office Action mailed November 28, 2008. An interview took place between the date of the Office Action and Response. One issue that was asked during the interview was whether or not the products of the present invention were an improvement over the prior art. In response to this issue raised, the Declaration of Dr. John D. Cleary was filed to show examples of the superior and unexpected results of the present invention. More specifically, this Declaration shows that the compositions of the present invention, when compared to commercial, USP preparations, demonstrated an ability to apply a 10-fold higher dose and obtain only about half the renal toxicity. Additionally, the Declaration shows that the mortality rate in infected mice treated with the claimed invention was about half the mortality rate of mice treated with commercial, USP preparations. Additionally, this trend occurs despite the 10-fold greater dose of the composition of the present invention. As indicated in the Declaration, this result is superior and unexpected.

Thus, in summary, Applicant has provided well-reasoned Declaration evidence that shows (i) that one of ordinary skill in the art would not view the references in the manner suggested in the Office Action, (ii) that the compositions of the present invention show superior and unexpected results when compared with formulations that are presently available, and (iii) the purification methods of the prior art would not result in compositions of the present invention.

There is no evidence of record rebutting any of the statements of the Declarations.

In view of the above, Applicants request that this rejection be withdrawn.

Petition for Extension of Time

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicants hereby petition for a three-month extension of time for filing a response to the outstanding Office Action. Payment for the extension of time fee is being submitted with the electronic filing of this response.

The Office is authorized to charge any deficiency or credit any overpayment associated with the filing of this application to Deposit Account 50-2752.

Finally, please contact the undersigned if there are any questions regarding this Amendment or the application in general.

Respectfully submitted,

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